REMARKS/ARGUMENTS

With entry of this amendment, claims 38-102 are pending. New claims 59-102 have been added. Claims 31-37 have been canceled without prejudice to Applicant's right to prosecute the subject matter of these claims in a related co-pending application. Claims 38-58 stand withdrawn.

New independent claims 59 and 81 correspond, in part, to previously presented claims 31, 33 and 37 and page 13, lines 19-23. The term "preventing" has been replaced with "prophylaxis" in the claims. Previous claim 31 referred to "treating" and "preventing" in the same claim. Because "prophylaxis" is a noun and "treating" is a verb, it is grammatically awkward to refer to both in the same claim. Accordingly, prophylaxis and treating are now claimed in two independent claims, 59 and 81, respectively. Support for prophylaxis is provided at *e.g.*, p. 35, lines 22-24.

Support for new claims 59 and 82 is provided at, *e.g.*, p. 10, line 29 through p. 11, line 1, p.14, lines 19-29, p. 15, lines 15-26, and p. 112, lines 12-15. Support for new claims 60 and 83 is provided at, *e.g.*, p. 38, lines 32-33. Support for new claims 61 and 84 is provided at, *e.g.*, p. 39, lines 4-10, and 19-20, and p. 40, lines 6-9. Support for new claims 62-70, and 85-93 is provided at, *e.g.*, p. 15, lines 1-8, p. 60, lines 13-17, and p. 66, lines 17-19. Support for new claims 71-78, and 94-102 is provided at, *e.g.*, p. 21, lines 2-3, and p. 29, lines 6-28. Support for new claims 80 and 103 is provided at, *e.g.*, p. 35, lines 22-25. Support for new claims 81 and 104 is provided at, *e.g.*, p. 11, lines 23-24 and p. 35, lines 19-24. No claim amendment or claim cancellation should be construed as an acquiescence in any ground of rejection.

Specification

¶8. Browser-Executable Code

Applicant has replaced the paragraph bridging pages 8 and 9 with a replacement in which the embedded hyperlink and/or other form of browser-executable code has been deleted.

¶9. Informalities

As requested by the Examiner the paragraphs beginning at p. 21, line 32; p. 24, line 17; p. 38, line 32; and, p. 41, line 10 of the specification have been replaced by replacement paragraphs which correct the various informalities.

Claim Rejections

35 U.S.C. § 112, first paragraph

Due to the length of the rejection, applicant addresses the Examiner's comments by paragraph using the numbering of the office action.

¶¶10-11. The Examiner summarizes the rejection and the claims. No response is needed other than to say that the new claims no longer recite a genus of 36 known diseases, but are directed to Alzheimer's disease, and the unnatural amino acid is specified as being a D amino acid.

¶12. The Examiner alleges that the PDAPP mouse is a model for Alzheimer's-type over-production of beta amyloid in the brain but not for Down's syndrome or other amyloidogenic disease. These comments are moot in view of amendment of the claims to recite Alzheimer's disease.

The Examiner also alleges the results in the PDAPP mouse are not representative of those in human citing to Munch. It is respectfully submitted that requiring a patent applicant to teach means for avoiding all side effects imposes too high a standard of enablement. Here, clinical trials have indicated that inflammatory side effects may result in a small number of patients (15 out of 360), as discussed in the Elan press releases (of record), and Munch. Moreover, in the few patients that might experience side effects, there is the possibility of mitigation by immunsuppressants (*see* Munch of record at p. 1085). Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Moreover, the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such

human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Id.*

¶13. The Examiner alleges that the specification does not provide enablement for each of the 36 amyloid-related disease. These remarks are moot in view of the new claims directed to Alzheimer's disease.

¶14. The Examiner alleges that "prevention" means total prevention, which the Examiner alleges is not enabled by the specification. In the context of preventive medicine, it is submitted that a regime does not have to achieve complete and total stoppage of disease in every patient to be considered a preventive treatment. Moreover, complete prevention was obtained in some experiments on the PDAPP mouse model. Nevertheless, to speed prosecution, applicants have replaced reference to prevention in the claims with "prophylaxis."

¶15. The Examiner summarizes the Wands factors bearing on enablement. No response is needed. The Examiner also reiterates comments from paragraph 13 regarding extrapolating from Aβ peptide to other peptides. These remarks are moot in view of the new claims as discussed above. The Examiner also refers to the guidance of the application in making substitutions of unnatural amino acids. These remarks are expounded at greater length by the Examiner in paragraphs 20-22 and will be addressed below.

¶16. The Examiner states that certain references are cited to illustrate the art of active immunization. No response is needed.

¶17. The Examiner cites Spooner as alleged evidence of deleterious side effects, and variability in the production of anti-Aβ antibodies. The issue of side effects has been addressed above. With respect to the Examiner's comment on variability of production, it is noted that data from a human clinical trial described in a declaration by Dr. Koller filed in related case 09/724,953 indicates that activity of immunization in inhibiting cognitive decline is not strongly correlated with titer of antibodies in a patient. Therefore, variability in antibody response between different patients does not preclude a beneficial response. Moreover, the antibody titer in a patient can be readily measured, and the dosage regime adjusted to achieve a desired titer (see specification at, e.g., p. 37, lines 19-20).

¶18. The Examiner cites Su as alleged evidence of side effects from administering Aβ to rats. Applicant reiterate the remarks above concerning side effects.

¶19. The Examiner refers to variations in prion-based diseases. These remarks are moot in view of the new claims directed to Alzheimer's disease.

¶¶20-22. The Examiner alleges that producing fragments and derivatives of each of the 36 amyloidogenic proteins involves unpredictability in view of the sometimes unpredictable effects of mutations on protein structure. The Examiner alleges that certain positions in the sequence are critical to protein structure and function, and that these can tolerate only conservative or no substitutions. The Examiner alleges that art-recognized procedures for producing and screening mutants for a therapeutic immune response are not adequate guidance. The Examiner alleges undue experimentation would be required in making and screening the alleged infinite number of possible molecules encompassed by the claims. In response, it is noted that these issue have at least in part been rendered moot in that the new claims are directed to Aβ fragments, and specify that the derivation with respect to the natural form of these fragments is the presence of at least one D amino acid.

Insofar as the rejection is directed to fragments, the specification provides several sources of evidence that N-terminal fragments are effective for treatment of Alzheimer's disease. First, the specification describes an example (*see* Example IV at p. 60 *et seq.*) in which Aβ1-5 was shown to reduce Aβ deposits in the cortex at statistically significant levels. Second, the specification provides data that three different monoclonal antibodies binding to epitopes 1-5, 3-6 or 3-7 bound to and phagocytosed amyloid deposits (*see* Example XII at p. 35 *et seq.*). One would expect that N-terminal fragments including epitopes 1-5, 3-6 or 3-7 would generate antibodies having similar specificity to the monoclonals found to induce phagocytosis amyloid deposits, and would therefore achieve similar results. Third, Example XVII at p. 101 *et seq.* provides data mapping the epitope specificity of antibodies induced by immunization with Aβ1-42 (*see* Example XVII at p. 101 *et seq.*). The data indicate the most of the antibodies bind to epitopes within Aβ1-11.

Collectively, these experiments show that fragments containing N-terminal epitopes can achieve a clearing response against amyloid deposits. Further, other fragments

could be screened using the same methods and same endpoints. The number of fragments of Aβ is not infinite and because many of the various possible fragments of beta amyloid peptide have overlapping sequences, the key regions of peptide needed for pharmacological activity can be determined by screening only a relatively small proportion of the total number of peptides. For example, if it is found that deletion of 20 amino acids from the C-terminus has no lowering of activity, then one can infer that deletions of fewer amino acids from the C-terminus will also not lower activity. Thus, by testing only a few of the possible fragments of beta amyloid peptide, one can predict whether any other fragment will have pharmacological activity. Therefore, it is submitted that undue experimentation would not be required to identify suitable fragments to use in the methods.

Similar considerations apply in testing variants of fragments in which at least one position is occupied by a D-amino acid. Again, the total number of possibilities is far from infinite. Moreover, screening can be simplified by optionally prescreening variants for reactivity with sera to Aβ before testing in a transgenic animal model (see specification at paragraph bridging pp. 17-18).

The Examiner appears to assume that a class of compounds having a desired activity cannot be enabled by the availability of screening methods to identify which compounds have the desired activity. However, *Wands* holds the opposite. The issue in *Wands* was whether the specification of the *Wands* patent enabled production of a class of antibodies having IgM isotype and a binding affinity of at least 10^9 M^{-1} using Kohler Milstein technology. As the Examiner is aware, Kohler Milstein technology is a classical technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired characteristics. The evidence indicated that only a small percentage of the hybridomas to be screened would produce antibodies having the desired property. Nevertheless, the court found that "practitioners of this art are prepared *to screen negative hybridomas in order to find one that makes the desired antibody*" (858 F.2d at 740, emphasis supplied). The *Wands* patent was held to be enabled.

The Examiner also appears to assume that enablement must be assessed from the perspective of screening each and every conceivable species falling within the claims. However, if the relevant quanta of experimentation for a genetic claim were the aggregate of work required to produce each and every embodiment potentially encompassed by the claim, it would never be possible to have a generic claim encompassing an unlimited number of species. Such claims have been upheld in numerous patents including those in unpredictable arts. *See, e.g., Ex parte Mark*, 12 USPQ2d 1904 (BPAI 1989); and, *In re Angstadt*, 190 USPQ 214 (CCPA 1976). The breadth of claims is relevant only insofar as the different species encompassed by the claims require different adaptations of an exemplified strategy. *See In re Strahilevitz*, 212 USPQ 561 (CCPA 1982) ("Although the invention is applicable to a large variety of haptens and antigens, the Examiner offered no reasons why these compounds would require *different techniques or process parameters*." *Ibid. at* p. 563 (emphasis supplied). Here, as discussed above, the application discloses a strategy of administering an agent and an adjuvant to generate antibodies against an amyloid component and thereby reducing or effecting prophylaxis of amyloid deposits. The application also shows how agents can be screened for the desired activity using a transgenic mouse model. The application exemplifies this strategy by generating antibodies using Aβ and certain fragments thereof. Other fragments and D-variants thereof can be identified by routine repetition of the same procedure. Routine repetition of the same basic procedures to isolate additional agents operating according to the same principles to achieve the same results may require considerable experimentation but does not constitute undue experimentation.

¶23. The Examiner cites Fonseca as teaching that antibodies raised against Aβ containing isoaspartic acid at position 7 will only bind the isoaspartic acid containing Aβ and not wildtype Aβ, from which the Examiner infers unpredictability as to whether antibodies activated by such a peptide will trigger an amyloid response against proteins absent any unnatural amino acids. In response, it is noted that in antibodies raised by Aβ peptides containing an isoaspartic acid can be effective either because they bind to normal Aβ or because they bind to the isoaspartic acid form of Aβ present in plaques. Thus, lack of binding of antibodies to normal Aβ

does not preclude pharmacological activity. Indeed, the present specification provides an example of an antibody that binds preferentially to a form of Aβ in which the asp residues at both positions 1 and 7 are isoaspartic acid. This antibody (22C8) showed positive results in clearing plaques in the PDAPP model (see specification at pp. 96-98). Similar considerations apply with respect to antibodies generated by D-forms of Aβ.

¶24. The Examiner cites references relating to toxicity of prion proteins as evidence of unpredictability. These comments are moot in view of amendment of the claims to recite Aβ peptide and treatment of Alzheimer's disease.

¶25. The Examiner cites Goldsby for the proposition that stimulation of an immune response does not necessarily mean that the patient has acquired protective immunity. It appears that the Examiner is alleging that a single treatment may not be enough to prevent disease development at all subsequent times. Applicant submits this is an overly high standard for any method, but is in any event moot in view of the new claims reciting prophylaxis rather than prevention. The Examiner also cites Goldsby as teaching that active immunization is not predictable as peptides are not generally immunogenic. In fact, Goldsby does not say that peptides are not generally immunogenic but only that they are not *as* immunogenic as proteins (p. 461, second column, first paragraph). Moreover, the immunogenicity of peptides can be increased using carriers as taught by the specification at e.g., pp. 28-32.

¶26. The Examiner cites Singh as teaching that inflammation may play a key role in Alzheimer's disease. The Examiner alleges that the specification only demonstrates successful antigenic presentation of a single peptide (i.e., Aβ42), presumably implying that administration of other peptides may cause inflammatory side effects. In response, Sing's comments are only an example of thinking in the art before those in the art became aware of the data in the present application. The data provided in the present application (and corresponding scientific publications by the present inventor) has changed the thinking in the art:

> The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse....Schenk's 1999 papers on the Elan vaccine created

> a sensation not least because the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.
>
> Washington Post , May 8, 2001 (copy attached).

Moreover, insofar as inflammation may occur as a side effect in a small number of patients, such is not detrimental to enablement as discussed in more detail above.

¶27. The Examiner cites Yang as teaching that the percentage of D amino acids in amyloid plaques increases with age, but that their role in pathogenesis of disease is not clear. The Examiner states that undue experimentation would be required in assessing the immunological significance and/or activity of each of the 34 possible unnatural amino acids. Insofar as the rejection is based on the possibility presence of 34 unnatural amino acids, it is moot in view of the amendment reciting D-amino acids. With respect to the role of D amino acids in pathogenesis, an understanding of this mechanism is not required to practice the invention. Regardless of the role, it is reasonable to expect that antibodies that bind to D-forms of Aβ will clear that Aβ in similar fashion to antibodies binding to L-forms of Aβ.

¶28. The Examiner cites Castillo as teaching that amylin is the causative agent in islet amyloid formation. The Examiner alleges undue experimentation in replacing each residue of the 37 protein with any one of 34 unnatural amino acid. These comments are moot in view of the new claims reciting Aβ peptide.

¶29. The Examiner merely summarizes the rejection. No additional comments are needed.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Medical Frontiers:
Confronting Alzheimer's

Promising Vaccine Targets Ravager of Minds

By Susan Okie
Washington Post Staff Writer
Tuesday, May 8, 2001; Page A01

TAMPA -- The moment he hits the cool water of the laboratory's baby pool, the brown mouse swims for dear life. He is 17 months old -- elderly for a mouse -- but he seems to have his goal in mind. He paddles to the center of the daisy-shaped water maze, looks around, then heads rapidly down the correct aisle and clambers to safety on an invisible platform.

An aging mouse's successful navigation of a maze might seem unconnected to the plight of the estimated 4 million Americans who have Alzheimer's disease, a common and incurable brain disorder that steals its victims' memories and personality. But maze-swimming mice here are testing a remarkable vaccine that one day may reduce or prevent brain damage from Alzheimer's, which is predicted to become epidemic as the nation's elderly population grows.

Mice at the University of South Florida have been given mutated human genes that produce age-related brain degeneration much like Alzheimer's disease. To the astonishment of scientists conducting the studies, vaccinating these mice during mid-life slowed progression of their brain disorder and preserved their ability to learn.

The vaccine, developed by California scientists with Elan Corp. of Dublin, Ireland, and now undergoing safety testing in people, is one of several promising new approaches being pursued for Alzheimer's disease, a disorder whose current treatments produce only partial and short-lived improvement. In a field where progress has been glacially slow for many years, scientists now speak of intense competition and rapidly emerging discoveries.

——Video——
• Post Reporter Dr. Sus
News Channel 8

——From Today's
• Aging Americans Are Healthier, Study Finds
Washington Post, May 8,
• Memory Lapse -- or A
(The Washington Post, Ma
• Expert Opinion: A Mat Degree
• Diagnostic Testing
• 10 Warning Signs of A
• The Time and Change

——More on Alzhei
• What is Alzheimer's D
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Exhibit F

"We tried about a dozen things that didn't work and now everything we're trying is working," said Dave Morgan, a neuroscientist at the University of South Florida who is testing the vaccine and other experimental treatments in transgenic mice. "I'm very encouraged."

The upsurge in innovative research stems in part from a clearer understanding of precisely what goes wrong in the brains of people with the disease. For example, researchers have identified two key enzymes that produce beta-amyloid, a waste protein that builds up in the brains of Alzheimer's victims and appears to be central to the destructive process. Several major drug companies are racing to identify and develop enzyme-blocking drugs called secretase inhibitors that they hope will reduce beta-amyloid accumulation. At least one company, Bristol-Myers Squibb Co., has begun testing such a drug in patients.

In addition, researchers are evaluating an array of compounds -- ranging from anti-inflammatory drugs, estrogen and cholesterol-lowering agents to various vitamins and supplements -- to see whether they can prevent Alzheimer's or delay its onset. Last month, in the first test of gene therapy for the disease, doctors in California implanted skin cells engineered to produce nerve growth factor into the brain of a woman with the disorder.

However, it may turn out that to stave off Alzheimer's disease, people will have to begin treatments such as the vaccine or enzyme-blockers in late middle age, perhaps a decade or two before symptoms would be expected to appear. At present, no medical test can predict who will develop the illness. Researchers say that if effective preventive treatments become available, such a test will be urgently needed.

A Stealthy Assault

Like AIDS, Alzheimer's is an ultimately fatal disorder that begins its stealthy assault years before problems with memory or learning make its presence apparent.

"The baby boomers are the people now getting Alzheimer's disease," said Trey Sunderland, chief of geriatric psychiatry at the National Institute of Mental Health (NIMH). "They just don't know it."

The biggest risk factor for Alzheimer's disease is growing old. The disorder is rare in people younger than 60, but its frequency doubles every five years after 65. By age 80, about 9 percent of people have the condition; by age 90, the prevalence is 29 percent. In the next half-century, as the elderly population grows, the number of Americans with Alzheimer's disease will roughly

quadruple. The total, estimated at between 2 million and 4 million now, is projected to be as high as 14 million by 2050.

The earliest sign that something is amiss in the brain is usually loss of recent memory. Later, people with the disease develop poor judgment, confusion and personality changes. They lose the ability to care for themselves and may fail to recognize their loved ones. Most live for an average of five to nine years with the illness, eventually becoming bedridden and dying of pneumonia or other infections.

Dorothy Ordway's husband and daughters first realized that she had Alzheimer's disease about six years ago, when the family rented a vacation house and Ordway kept forgetting where her bedroom was. A former banker, she was also neglecting to pay her bills.

For several years, Ordway, 80, attended a senior day care center and continued to live in her Parkville, Md., home, but she grew increasingly confused.

"She thought I was her father," recalled her husband, Thomas, 85. Last summer, after she began leaving the stove on, her family was forced to move her to an assisted-living facility.

"She knows that she's not home, but she doesn't know where she is," said her daughter, Nancy Barlow. "The day before yesterday, I'm not sure she could have told you what my name was . . . I really sensed for the first time that she wasn't quite sure."

For the family, Barlow added, watching her mother's decline "is a grieving process."

Under a microscope, the brain of someone who has died of Alzheimer's disease resembles a junkyard. Scattered among the surviving nerve cells of the cerebral cortex -- the cells responsible for thoughts, learning and decisions -- are myriad clumps or "plaques" of beta-amyloid, a waste protein toxic to nerve cells that is a hallmark of the illness. Around the plaques cluster disease-fighting cells that seem to be trying unsuccessfully to clean up or wall off the mess. Everywhere are misshapen pieces of dead nerve cells, their insides choked with tangles made of a twisted, cable-like protein called tau.

"Nerves die and all you have left are the tangles," said pathologist Juan C. Troncoso of Johns Hopkins School of Medicine as he examined such a brain. "What we're not seeing here is perhaps what is most important." The tissue specimen showed few synapses, the connections between nerve cells through which they communicate. A healthy brain cell typically has as many as 15,000 synapses with other cells. "These individuals have a tremendous amount of synaptic loss," Troncoso said.

The Vaccine Inspiration

Faced with such wreckage, researchers have tried for years to determine what

sets off the destruction -- and in particular, whether amyloid plaques or tau tangles are the primary trigger. Although both appear to contribute, experts said there is now convincing evidence that buildup of beta-amyloid is at the root of the disease.

Key to this conclusion was the discovery of three human genes that, when mutated, have been found to cause inherited Alzheimer's in rare families. All three genes are involved in making beta-amyloid. One contains the code for a larger protein that is snipped apart to produce the toxic fragment; the other two carry instructions for an enzyme that does some of the snipping.

"Every known mutation ultimately increases" buildup of beta-amyloid, Morgan said.

Once these genes were identified, scientists began introducing mutated versions into the fertilized eggs of mice, hoping to engineer a mouse strain that would develop something similar to Alzheimer's disease. By the mid-1990s, scientists at Elan's laboratories in South San Francisco had such a strain and wanted to devise experiments that might lead to diagnostic tests or treatments.

At that point, biochemist Dale Schenk had an idea that he calls "a little bit crazy." Why not try vaccinating the mice against beta-amyloid?

Schenk reasoned that the protein accumulated in the brain because it was being produced faster than it was removed. He thought that if he could stimulate the immune system to make antibodies, proteins that would stick to beta-amyloid and tag it as an unwanted substance, they might shift that balance, perhaps reducing or preventing the buildup.

The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse.

"It was breaking a lot of paradigms," Schenk acknowledged. "I had a lot of arguments with my colleagues. . . . This experiment ended up at the absolute bottom of the priority list of things to do."

Schenk first vaccinated six-week-old transgenic mice and found that the vaccine completely protected them from developing amyloid plaques. Even when the vaccine was given to older animals that already had plaques in their brains, it reduced the appearance of additional plaques and seemed to make some of the existing beta-amyloid deposits disappear. Under the microscope, it appeared that microglial cells -- wandering brain cells that clean up debris and fight infection -- were becoming activated by the vaccine and gobbling up the plaques.

"That was a major surprise," Schenk recalled.

Schenk's 1999 paper on the Elan vaccine created a sensation, not least because

the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.

But no one knew whether the treatment could improve learning or memory in affected animals. Without such evidence, medical researchers would be reluctant to try it in people. "You may remove the amyloid, but patients may not do any better," noted Hopkins' Troncoso.

Using the Florida transgenic mice, Morgan and his team tried to address that question. They used a water maze shaped like a daisy with six petals to test animals' "working memory": the ability to learn and remember new information, which is the earliest brain function affected by Alzheimer's.

Each day, the escape platform is placed at the end of a different arm of the maze. A mouse must swim until it locates the platform, which is invisible from the surface. Mice in the experiment were given five trials each day, testing their ability to learn and recall the platform's location. The next day, the platform was moved to a new location.

"It's like you have to remember where you parked your car," said David Diamond, a behavioral neuroscientist who designed the water maze used in the study.

Morgan and his colleagues gave transgenic animals monthly injections of a vaccine similar to the one developed by Elan, starting at seven months of age. He first tested them in the maze when they were 11 months old, expecting that brain inflammation caused by the vaccine would worsen their performance. Instead, they learned the maze as fast as normal mice. "We were completely wrong," he said. "They were just dynamite."

By 15 months of age, transgenic mice that had not gotten the vaccine had developed severe brain disease and could no longer navigate the maze. But the vaccine recipients could still learn and remember the platform's location, although they took longer to master it than normal animals. Morgan and his team are now studying whether the vaccine still protects the brain when the treatment is begun later in the animals' lives.

Testing in Humans

The Florida team's promising findings and those of another group in Canada have spurred Elan's efforts to test the vaccine in Alzheimer's patients. Last year, a small safety study in this country found no significant side effects. The vaccine is now undergoing a multidose safety trial involving about 80 patients in Great Britain who have mild or moderate Alzheimer's disease. The results are expected within the next two months. If they are favorable, the company hopes to begin testing the vaccine in a larger number of patients to see whether it has a favorable impact on their illness.

"I think it provides some hope," said Schenk, who is to receive a prize for his discovery today at the American Academy of Neurology's annual meeting.

Many researchers are nervous about the prospect of giving a vaccine to activate the immune system in the brain, reasoning that if it triggers inflammation or other adverse effects, doctors won't be able to turn off the process. Some have suggested it might be safer simply to give patients periodic injections of antibodies against beta-amyloid -- much as gamma globulin shots were once given to prevent hepatitis -- because the treatment could be stopped if side effects developed.

The NIMH's Sunderland, who is trying to develop a predictive test for Alzheimer's disease, is studying a group of healthy volunteers who are at higher-than-average risk because they have parents or siblings with the disorder.

"They ask, 'Should I get the vaccine?'" Sunderland said. "My opinion is, 'No. Not now.' "

Nevertheless, Sunderland said he is encouraged by the results so far. He said he suspects that an Alzheimer's vaccine may work better for preventing the disease than for treating it once the brain has become severely affected.

"Let's say they give it to Alzheimer's patients and it fails," he said. "It might seem a devastating blow to the vaccine concept, but maybe they gave it to the wrong people. Right now, there is no flashlight . . . telling you where to point your treatment, and when."